

Hepatocellular Carcinoma Risk in Advanced Fibrosis After Sustained Virologic Response: When Can We Safely Stop Hepatocellular Carcinoma Surveillance?

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Chronic infection caused by hepatitis C virus (HCV) affects approximately 58 million people worldwide and is responsible for an estimated 290,000 deaths annually from complications of end-stage liver disease, including hepatocellular carcinoma (HCC).⁽¹⁾ Since the approval of the highly effective direct-acting antivirals in 2013–2014,^(2,3) approximately 10 million people have been

treated and had achieved sustained virologic response (SVR) by the end of 2019. Eradication of HCV significantly reduces but does not eliminate the risk of HCC among those with advanced liver fibrosis or cirrhosis.

While there is general consensus that those with cirrhosis should undergo continued HCC surveillance posttreatment, there are discrepant recommendations among major international guidelines for those without cirrhosis. According to the American Association for the Study of Liver Diseases⁽⁴⁾ and European Association for the Study of the Liver,⁽⁵⁾ patients with advanced liver fibrosis or cirrhosis (METAVIR score F3–F4) should continue undergoing surveillance for HCC every 6 months with ultrasound testing; patients without advanced fibrosis (METAVIR score F0–F2) and who achieved SVR do not require continued HCC surveillance. In contrast, the Asian Pacific Association for the Study of the Liver⁽⁶⁾ recommends that even patients without advanced fibrosis or cirrhosis should continue HCC surveillance indefinitely and at 6-month intervals within 2 years after the end of treatment and at 12-month intervals thereafter. The Japan Society of Hepatology⁽⁷⁾ also states that follow-up for hepatocarcinogenesis needs to be performed even after HCV clearance. There is currently no guidance on when to discontinue surveillance if started after HCV clearance. The discrepancy in these recommendations may be driven, at least in part, by the difference in the incidence of HCC between the East and West. In Japan, HCC develops at an annual rate of 5%–7% in patients with HCV-related cirrhosis compared with 1%–4% in the United States and Europe.

In this issue of *Hepatology Communications*, Tamaki et al.⁽⁸⁾ reported the results of a nationwide multicenter

Abbreviations: AFP, α -fetoprotein; FIB-4, fibrosis-4; GAF, gamma-glutamyl transpeptidase, α -fetoprotein, fibrosis-4; GGT, gamma-glutamyl transpeptidase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

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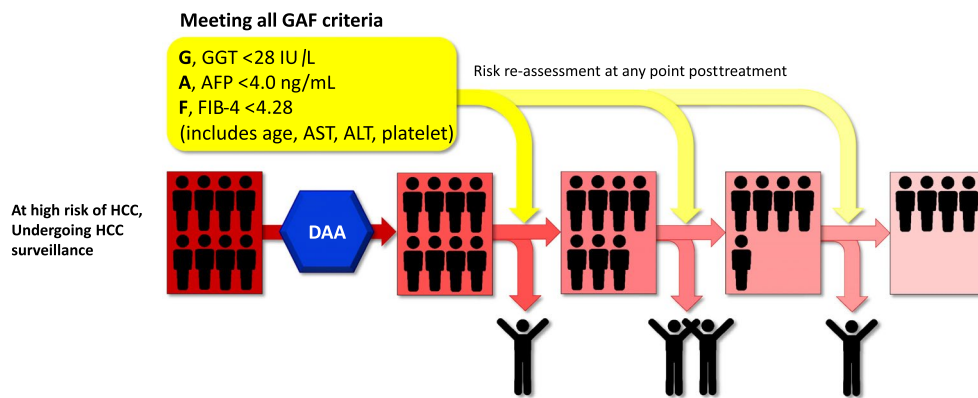


FIG. 1. The HCC risk model. GAF criteria based on gamma-glutamyl transpeptidase, AFP, and FIB-4 index at any point after SVR can help identify patients at negligible risk of developing HCC who may be able to discontinue HCC surveillance. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral.

study to develop a simple serum-based HCC risk model that can identify patients at negligible risk of developing HCC. The study consisted of a derivation cohort, comprising 1,325 patients (533 men and 792 women) with a median age of 72 years (interquartile range [IQR], 64–77 years) with advanced fibrosis or cirrhosis (defined as fibrosis-4 [FIB-4] index ≥ 3.25 or F3–F4) who achieved SVR from the Japanese Red Cross Hospital Liver Study Group registry, and a validation cohort comprising 508 patients (210 men and 298 women) with a median age of 74 years (IQR, 67–79 years) from two other institutes. In the derivation and validation cohorts, 73 (5.5%) and 54 (10.6%) patients developed HCC during a median follow-up duration of 2.96 and 3.65 years, respectively. Based on the multivariable analysis, patients fulfilling all criteria (gamma-glutamyl transpeptidase [GGT] <28 IU/L, α -fetoprotein [AFP] <4.0 ng/mL, and FIB-4 index <4.28 [GAF criteria]) were classified as having a negligible risk of developing HCC (0.5–1.1/100 person-years in the derivation cohort and 0.9–1.1/100 person-years in the validation cohort; Fig. 1). Patients were also reclassified with regards to their HCC risk during follow-up. Among patients who were high risk at baseline (i.e., did not meet all the GAF criteria based on laboratory values at SVR) who later fulfilled the GAF criteria during follow-up, the overall HCC incidence was also low at 0.6/100 person-years in the derivation cohort and 1.1/100 person-years in the validation cohort. The HCC risk model demonstrated

consistent findings in subgroup analyses stratified by age (<70, 70-79, and ≥80 years) and sex. The authors concluded that this HCC risk model, based on readily available and serum markers, can help identify patients at negligible risk of developing HCC and who may not need HCC surveillance.

Previous studies identified the risk factors for the occurrence of HCC in patients with SVR after treatment. These included older age; male sex; advanced liver fibrosis, morbidities, such as metabolic syndrome and alcohol consumption; and serum AFP levels.⁽⁶⁾ One of the strengths of this GAF model is that it consists of only three variables, GGT, AFP, and FIB-4 index, which are readily available in clinical practice and do not require any specialized equipment for collection. The FIB-4 index is a well-validated index for the noninvasive assessment of liver fibrosis, including patient age, aspartate and alanine aminotransferase levels, and platelet count, and is also a strong predictor of HCC risk. GGT has been widely used as a marker of liver injury, counteracting oxidative stress by enabling the extracellular metabolism of glutathione. Elevated GGT levels reflect pro-oxidant activity and cellular damage, especially in patients with metabolic syndrome or excess alcohol consumption habit. Serum GGT levels are usually higher in men than in women. AFP is a well-known tumor-associated antigen that can also be used as a surrogate marker to predict various precancerous conditions, including inflammation, fibrosis, and liver regeneration. In previous studies,

posttreatment AFP level is a better predictor of HCC development than pretreatment AFP level because pretreatment levels can be elevated in the setting of active viral inflammation.

Despite significant delays in HCV treatments due to the coronavirus disease 2019 pandemic,⁽⁹⁾ millions of infected people will continue to be treated and attain SVR annually. The total number of patients who achieved HCV clearance will continue to increase year by year, and the HCC risk among these treated patients may decline over time, provided they have no comorbidities, such as metabolic syndrome or harmful alcohol consumption. As the HCC risk decreases, there may be a risk threshold following which HCC surveillance may be discontinued. A strength of this model is that risk assessment can be repeated following HCV clearance to determine whether HCC surveillance can be discontinued. Recently, a cost-effectiveness analysis indicated that HCC risk needs to be >1.32% per year for HCC surveillance after SVR to be cost effective.⁽¹⁰⁾ It may be reasonable to discontinue HCC surveillance for patients who were reclassified to being at low risk by the GAF criteria (HCC risk, 0.6–1.3/100 person-years) in terms of cost effectiveness.

There are potential study limitations. This study was conducted in Japan where patients are older and consequently have high HCC risk; however, the risk model can be easily validated and applied to patients with eradicated HCV in other regions of the world. In addition, the observation period of the study was relatively short. Further long-term studies in different regions of the world are necessary to validate the utility of this HCC risk model.

In summary, this HCC model based on GAF criteria can identify patients at low risk of developing HCC after HCV eradication and who may not need HCC surveillance. The model is also dynamic. Changes in the GAF criteria over time can help identify patients who may be able to discontinue HCC surveillance.

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REFERENCES

- 1) World Health Organization. Hepatitis C. <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>. Published July 27, 2021. Accessed September 2021.
- 2) Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al.; POSITRON Study; FUSION Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368:1867–1877.
- 3) Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014;59:2083–2091.
- 4) Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatology* 2020;71:686–721.
- 5) European Association for the Study of the Liver. Clinical Practice Guidelines Panel: Chair; EASL Governing Board representative; Panel members. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol* 2020;73:1170–1218.
- 6) Kanda T, Lau GKK, Wei L, Moriyama M, Yu M-L, Chuang W-L, et al. APASL HCV guidelines of virus-eradicated patients by DAA on how to monitor HCC occurrence and HBV reactivation. *Hepatol Int* 2019;13:649–661.
- 7) Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update. *Hepatol Res* 2020;50:791–816.
- 8) Tamaki N, Kurosaki M, Yasui Y, Mori N, Tsuji K, Hasebe C, et al. Hepatocellular carcinoma risk assessment for patients with advanced fibrosis after eradication of hepatitis C virus. *Hepatol Commun* 2021. <https://doi.org/10.1002/hep4.1833>.
- 9) Farhang Zangneh H, Wong WWL, Sander B, Bell CM, Mumtaz K, Kowgier M, et al. Cost effectiveness of hepatocellular carcinoma surveillance after a sustained virologic response to therapy in patients with hepatitis C virus infection and advanced fibrosis. *Clin Gastroenterol Hepatol* 2019;17:1840–1849.e16.
- 10) Blach S, Kondili LA, Aghemo A, Cai Z, Dugan E, Estes C, et al. Impact of COVID-19 on global HCV elimination efforts. *J Hepatol* 2021;74:31–36.